Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections.

Bibliographic Source(s)

Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, McFarland LV, Mellow M, Zuckerbraun BS. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Am J Gastroenterol. 2013 Apr;108(4):478-98. [253 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Definitions for quality of evidence (High, Moderate, Low) and strength of recommendation (Strong, Conditional) are given at the end of the "Major Recommendations" field.

Summary and Strength of Recommendations

Diagnostic Tests

1. Only stools from patients with diarrhea should be tested for *Clostridium difficile*. (Strong recommendation, high-quality evidence)
2. Nucleic acid amplification tests (NAAT) for *C. difficile* toxin genes such as polymerase chain reaction (PCR) are superior to toxins A+B enzyme immunoassay (EIA) testing as a standard diagnostic test for *C. difficile* infection (CDI). (Strong recommendation, moderate-quality evidence)
3. Glutamate dehydrogenase (GDH) screening tests for *C. difficile* can be used in two- or three-step screening algorithms with subsequent toxin A and B EIA testing, but the sensitivity of such strategies is lower than NAATs. (Strong recommendation, moderate-quality evidence)
4. Repeat testing should be discouraged. (Strong recommendation, moderate-quality evidence)
5. Testing for cure should not be done. (Strong recommendation, moderate-quality evidence)

Management of Mild, Moderate, and Severe CDI

6. If a patient has strong a pre-test suspicion for CDI, empiric therapy for CDI should be considered regardless of the laboratory testing result, as the negative predictive values for CDI are insufficiently high to exclude disease in these patients. (Strong recommendation, moderate-quality evidence)

7. Any inciting antimicrobial agent(s) should be discontinued, if possible. (Strong recommendation, high-quality evidence)
8. Patients with mild-to-moderate CDI should be treated with metronidazole 500 mg orally three times per day for 10 days. (Strong recommendation, high-quality evidence)
9. Patients with severe CDI should be treated with vancomycin 125 mg four times daily for 10 days (Conditional recommendation, moderate-quality evidence)
10. Failure to respond to metronidazole therapy within 5–7 days should prompt consideration of a change in therapy to vancomycin at standard dosing. (Strong recommendation, moderate-quality evidence)
11. For mild-to-moderate CDI in patients who are intolerant/allergic to metronidazole and for pregnant/breastfeeding women, vancomycin should be used at standard dosing. (Strong recommendation, high-quality evidence)
12. In patients in whom oral antibiotics cannot reach a segment of the colon, such as with Hartman's pouch, ileostomy, or colon diversion, vancomycin therapy delivered via enema should be added to treatments above until the patient improves. (Conditional recommendation, low-quality evidence)
13. The use of anti-peristaltic agents to control diarrhea from confirmed or suspected CDI should be limited or avoided, as they may obscure symptoms and precipitate complicated disease. Use of anti-peristaltic agents in the setting of CDI must always be accompanied by medical therapy for CDI. (Strong recommendation, low-quality evidence)

Management of Severe and Complicated CDI

14. Supportive care should be delivered to all patients and includes intravenous fluid resuscitation, electrolyte replacement, and pharmacological venous thromboembolism prophylaxis. Furthermore, in the absence of ileus or significant abdominal distention, oral or enteral feeding should be continued. (Conditional recommendation, low-quality evidence)
15. Computerized tomography (CT) scanning of the abdomen and pelvis is recommended in patients with complicated CDI. (Conditional recommendation, low-quality evidence)
16. Vancomycin delivered orally (125 mg four times per day) plus intravenous metronidazole (500 mg three times a day) is the treatment of choice in patients with severe and complicated CDI who have no significant abdominal distention. (Strong recommendation, low-quality evidence)
17. Vancomycin delivered orally (500 mg four times per day) and per rectum (500 mg in a volume of 500 ml four times a day) plus intravenous metronidazole (500 mg three times a day) is the treatment of choice for patients with complicated CDI with ileus or toxic colon and/or significant abdominal distention. (Strong recommendation, low-quality evidence)
18. Surgical consult should be obtained in all patients with complicated CDI. Surgical therapy should be considered in patients with any one of the following attributed to CDI: hypotension requiring vasopressor therapy; clinical signs of sepsis and organ dysfunction (renal and pulmonary); mental status changes; white blood cell count ≥50,000 cells/μl, lactate ≥5 mmol/l; or failure to improve on medical therapy after 5 days. (Strong recommendation, moderate-quality evidence)

Management of Recurrent CDI (RCDI)

19. The first recurrence of CDI can be treated with the same regimen that was used for the initial episode. If severe, however vancomycin should be used. The second recurrence should be treated with a pulsed vancomycin regimen. (Conditional recommendation, low-quality evidence)
20. If there is a third recurrence after a pulsed vancomycin regimen, fecal microbiota transplant (FMT) should be considered. (Conditional recommendation, moderate-quality evidence)
21. There is limited evidence for the use of adjunct probiotics to decrease recurrences in patients with RCDI. (Moderate recommendation, moderate-quality evidence)
22. No effective immunotherapy is currently available. Intravenous immune globulin (IVIG) does not have a role as sole therapy in treatment of RCDI. However, it may be helpful in patients with hypogammaglobulinemia. (Strong recommendation, low-quality evidence)

Management of Patients with CDI and Co-morbid Conditions

23. All patients with inflammatory bowel disease (IBD) hospitalized with a disease flare should undergo testing for CDI. (Strong recommendation, high-quality evidence)
24. Ambulatory patients with IBD who develop diarrhea in the setting of previously quiescent disease, or in the presence of risk factors such as recent hospitalization, or antibiotic use, should be tested for CDI. (Strong recommendation, moderate-quality evidence)
25. In patients who have IBD with severe colitis, simultaneous initiation of empiric therapy directed against CDI and treatment of an IBD flare may be required while awaiting results of *C. difficile* testing. (Conditional recommendation, low-quality evidence)
26. In patients with IBD, ongoing immunosuppression medications can be maintained in patients with CDI. Escalation of immunosuppression medications should be avoided in the setting of untreated CDI. (Conditional recommendation, low-quality evidence)

27. Patients with IBD who have a surgically created pouch after colectomy may develop CDI and should be tested if they have symptoms. (Strong recommendation, moderate-quality evidence)
28. Underlying immunosuppression (including malignancy, chemotherapy, corticosteroid therapy, organ transplantation, and cirrhosis) increases the risk of CDI, and such patients should be tested if they have a diarrheal illness. (Strong recommendation, moderate-quality evidence)
29. Any diarrheal illness in women who are pregnant or periparturient should prompt testing for *C. difficile*. (Conditional recommendation, low-quality evidence)

Infection Control and Prevention

30. A hospital-based infection control programs can help to decrease the incidence of CDI. (Conditional recommendation, moderate-quality evidence)
31. Routine screening for *C. difficile* in hospitalized patients without diarrhea is not recommended and asymptomatic carriers should not be treated. (Strong recommendation, low-quality evidence)
32. Antibiotic stewardship is recommended to reduce the risk of CDI. (Strong recommendation, high-quality evidence)
33. Contact precautions for a patient with CDI should be maintained at a minimum until the resolution of diarrhea. (Strong recommendation, high-quality evidence)
34. Patients with known or suspected CDI should be placed in a private room or in a room with another patient with documented CDI. (Strong recommendation, high-quality evidence)
35. Hand hygiene and barrier precautions, including gloves and gowns, should be used by all health-care workers and visitors entering the room of any patient with known or suspected CDI. (Strong recommendation, moderate-quality evidence)
36. Single-use disposable equipment should be used for prevention of CDI transmission. Non-disposable medical equipment should be dedicated to the patient's room and other equipment should be thoroughly cleaned after use in a patient with CDI. (Strong recommendation, moderate-quality evidence)
37. Disinfection of environmental surfaces is recommended using an Environmental Protective Agency (EPA)-registered disinfectant with *C. difficile*-sporicidal label claim or 5000 p.p.m. chlorine-containing cleaning agents in areas of potential contamination by *C. difficile*. (Strong recommendation, high-quality evidence)
38. Although there is moderate evidence that two probiotics (*Lactobacillus rhamnosus* GG and *Saccharomyces boulardii*) decrease the incidence of antibiotic associated diarrhea, there is insufficient evidence that probiotics prevent *C. difficile* infection. (Strong recommendation, low-quality evidence)

Definitions:

Quality of Evidence

High: Further research is unlikely to change confidence in the estimate of the effect.

Moderate: Further research is likely to have an important impact and may change the estimate.

Low: Further research is very likely to change the estimate.

Strength of Recommendation

Strong: The evidence shows the benefit of the intervention or treatment clearly outweighs any risk.

Conditional: Uncertainty exists about the risk–benefit ratio.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Clostridium difficile infection (CDI)

Guideline Category

Diagnosis

Management

Prevention

Treatment

Clinical Specialty

Family Practice

Gastroenterology

Infectious Diseases

Internal Medicine

Preventive Medicine

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide recommendations for the diagnosis and management of patients with *Clostridium difficile* infection (CDI) as well as for the prevention and control of outbreaks while supplementing previously published guidelines

Target Population

Patients with *Clostridium difficile* infection (CDI)

Interventions and Practices Considered

Diagnosis

1. Nucleic acid amplification tests (NAAT)
2. Glutamate dehydrogenase (GDH) screening tests

Management/Treatment

1. Empiric therapy
2. Discontinuation of inciting antimicrobial agent(s)
3. Metronidazole (in mild-to-moderate *Clostridium difficile* infection [CDI])
4. Vancomycin (in severe CDI)
5. Intravenous fluid resuscitation
6. Electrolyte replacement

7. Pharmacological venous thromboembolism prophylaxis
8. Computerized tomography (CT) scanning of the abdomen and pelvis
9. Surgical therapy
10. Fecal microbiota transplant (FMT)

Prevention

1. Hospital-based infection control programs
2. Antibiotic stewardship
3. Contact precautions
4. Quarantine
5. Hand hygiene and barrier precautions
6. Single-use disposable equipment
7. Disinfection of environmental surfaces

Major Outcomes Considered

- Rates of *Clostridium difficile* infection (CDI)
- Length of hospital stay

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Database(s) searched: MEDLINE, PubMed, Google Scholar. Searches were performed for the years 1975–2012. Search terms included: "epidemiology", "risk factors", "Clostridium difficile infections", "colitis", "PMC", "antibiotics", "antibiotic-associated diseases", "incidence and C. difficile", "prevalence and C. difficile", "demographics and C. difficile", "PCR", "glutamate dehydrogenase", "cytotoxin", "NAAT", "vancomycin", "metronidazole", "fidaxomicin", "C. difficile surgery", "C. difficile fulminant", "C. difficile and IBD or ulcerative colitis or Crohn's disease of inflammatory bowel disease or liver disease or cirrhosis or pregnancy or transplantation", "probiotics", "recurrent CDI", "relapsing CDI", "fecal transplant", "stool transplant", "fecal microbiota transplant", "C. difficile incidence", "community-acquired C. difficile", "hospital-associated infections", "hospital-acquired infections", "C. difficile culture", "toxigenic culture", "rifampin", "rifaximin", "antibiotic resistance", "infection control", "infection prevention", "contact precautions", and "isolation precautions". Selected cited references were investigated and certain authors were contacted for further information.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to grade the quality of evidence.

High: Further research is unlikely to change confidence in the estimate of the effect.

Moderate: Further research is likely to have an important impact and may change the estimate.

Low: Further research is very likely to change the estimate.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

See the "Rating Scheme for the Strength of the Evidence" field.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

See the "Rating Scheme for the Strength of the Recommendations" field.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendation

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to grade the strength of recommendations.

Strong: The evidence shows the benefit of the intervention or treatment clearly outweighs any risk.

Conditional: Uncertainty exists about the risk–benefit ratio.

Cost Analysis

Clostridium difficile infection (CDI) is a leading cause of hospital-associated gastrointestinal illness and places a high burden on our health-care system, with costs of 3.2 billion dollars annually.

Cost of Antibiotic Therapy for *C. difficile*

	Cost per Dose	Regimen	Cost per 10-day Regimen
Metronidazole 500 mg	$0.73	500 mg three times a day	$22.00
Vancomycin	$17.00	125 mg four times a day	$680.00

125 mg pills	Cost per Dose	Regimen	Cost per 10-day Regimen
Vancomycin 125 mg IV compounded for oral	$2.50–$10.00	125 mg four times a day	$100.00–$400.00
Fidaxomicin 200 mg	$140.00	200 mg twice a day	$2,800.00

IV = intravenous.

Vancomycin IV form can be compounded for oral use as well as used for enema therapy.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

In an effort to make our new guidelines as "fresh" as possible when published, we have created a special guideline review process, involving members of the Board of Trustees, Practice Parameters Committee and the American Journal of Gastroenterology. It is our goal to review the guideline, allow you to revise the guideline, and re-review the guideline within 6 months of first submission. Therefore the entire process should take 1 year from commission to finished, accepted guideline.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Appropriate diagnosis, treatment and prevention of *Clostridium difficile*.
- It has become evident that surgery is of benefit to patients at the advanced extreme of *C. difficile* infection (CDI), and early surgical consultation has been associated with improved survival.
- Several published case reports suggest open-label benefit of intravenously administered tigecycline as a rescue strategy for the treatment of patients with severe CDI, in whom therapy with vancomycin and metronidazole has failed.

Potential Harms

- The Infectious Disease Society of America (IDSA)/Society of Hospital Epidemiologists of America (SHEA) guidelines included a C-III recommendation to "avoid [the] use of antiperistaltic agents, as they may obscure symptoms and precipitate toxic megacolon." A literature review of 55 patients with *Clostridium difficile* infection (CDI) who were exposed to such agents found that 17 patients developed colonic dilatation and 5 died. All of these adverse outcomes, however, occurred in patients with CDI who initially received treatment with antiperistaltic agents alone. All 23 patients in this review who received antiperistaltic agents only in combination with CDI antimicrobial

therapy survived.

- Fecal microbiota transplant (FMT) appears to be safe, with no adverse effects or complications directly attributed to the procedure yet described in the existing literature. The potential for transmission of infectious agents is a concern, however, and a recent publication outlines rigorous screening of stool donors' blood and stool for common bacterial and viral enteropathogens. In July 2013, the U.S. Food and Drug Administration (FDA) released a policy on FMT (see the Federal Register for details).

Contraindications

Contraindications

Metronidazole treatment should be avoided in pregnancy and breastfeeding. First trimester exposure to metronidazole is not recommended in U.S. Food and Drug Administration (FDA) guidelines because of concern regarding ready placental transmission and case reports describing facial anomalies following exposure. Metronidazole and its active metabolites are readily detected in breast milk and in the plasma of infants.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Patient Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, McFarland LV, Mellow M, Zuckerbraun BS. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Am J Gastroenterol. 2013 Apr;108(4):478-98. [253 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Apr

Guideline Developer(s)

American College of Gastroenterology - Medical Specialty Society

Source(s) of Funding

American College of Gastroenterology

Guideline Committee

Not stated

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Financial support: None.

Potential competing interests: Dr. Ananthakrishnan is on the scientific advisory boards for Prometheus Laboratory and Janssen; Dr. Binion has received honoraria and is a consultant for Optimer, Janssen, Abbott, Salix, UCB Pharma, and Given Imaging; Dr. Brandt is on the speaker's bureau has received grant funding from Optimer; Dr. Gilligan's research was funded by Remel Lenexa, KS, Meridian Bioscience, Cincinnati, OH, Cepheid, Sunnyvale, CA, and TechLab, Blacksburg, VA, and has received honorarium from Alere Scarborough, ME; Dr. Mellow is on the speaker's bureau of Optimer; Dr. Zuckerbraun is on the speaker's bureau of Pfizer; Dr. McFarland is on the advisory board of BioK Canada; Dr. McFarland is a Government employee. The remaining authors declare no conflict of interest.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the American College of Gastroenterology (ACG) Web site .

Availability of Companion Documents

The following is available:

- American College of Gastroenterology Practice Parameters Committee. Guideline development policies. 2010 Jan. Available from the American College of Gastroenterology (ACG) Web site .

Patient Resources

Information on *Clostridium Difficile* infection is available from the American College of Gastroenterology's Patient Education & Resource Center Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on June 27, 2013. The information was verified by the guideline developer on July 23, 2013.

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